REMARKS

Reconsideration is requested.

Claims 1-67, 71-72, 75, 80-84 and 92-94 have been canceled, without prejudice. Claims 97-101 have been added. Support for the amended claims may be found throughout the specification. No new matter has been added. Claims 68-70, 73-74, 76-77, 79, 85-91 and 96-101 are pending.

The figures have been amended to include the attached formal drawings.

Reconsideration and withdrawal of the restriction requirement is again requested by the attached Petition. Consideration of the attached Petition and a Decision on the same are requested prior to the Examiner issuing a further Action on the merits. Consideration of the attached Petition and a decision on the same prior to issuance of a further Action on the merits will advance prosecution by defining the subject matter of any further search.

The applicants have cited art from a parent application which includes PCT application which the Examiner has indicated can not be considered because the Patent Office has been unable to maintain the files of the Patent Office in such a way that the art from the parent application is available to the Examiner. The applicants note that the inability of the Patent Office to maintain its files in this regard places a serious burden on the applicants in having to continually provide further copies of documents in subsequent files. The Rules in the MPEP provide for the Patent Office to have responsibility to maintain its files to reduce this burden on the applicants. Moreover, the Patent Office resources are far greater than the applicants such that the Patent Office would appear to be able to obtain further copies of art, especially published PCT

applications, through, for example either the Patent Office or outside sources for any references they may lose or misplace. Further copies of the previously cited documents will be filed under separate cover once obtained by the undersigned and consideration and return of an initialed copy of the previously filed PTO-1449 Form, pursuant to MPEP §609, are requested.

To the extent not obviated by the above, the Section 112, second paragraph, rejection of claims 67-70, 73-74, 76-77, 79 and 85-86 stated on page 3 of Paper No. 18 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

With regard to paragraph 6 of Paper No. 18, claims 67 has been canceled. The rejection stated therein is therefore moot. The remaining claims are submitted to be definite. One or ordinary skill in the art will appreciate that a nucleotide sequence allowing the expression of an HCV E1 protein is a nucleotide sequence at least containing an open reading frame of a HCV E1 envelope protein wherein the HCV E1 envelope protein is as defined in the specification. The metes and bounds of the claims are submitted to be definite.

With regard to the Examiner's comments in paragraph 7 of Paper No. 18, the applicants respectfully refer to the Examiner to paragraph 16 of Paper No. 18 wherein the Examiner refers to Matsuura (Journal of Virology, 1992, Volume 66, pages 1425-1431), wherein the Examiner apparently has had little difficulty understanding the conventional representations of one of ordinary skill in this art and orientations described by those of ordinary skill in the art. The applicants have used similarly recognized language known to those of ordinary skill in the art. Reconsideration and

withdrawal of the rejection are requested. The applicants note the Examiner's reference to claim "58" in paragraph 7 of Paper No. 18 is not clear as claim 58 is not pending and was not pending at the time the Paper No. 18 was issued. Clarification is requested in this regard in the event the rejection is maintained.

With regard to the Examiner's comments in paragraph 8 of Paper No. 18, the applicants submit that the HCV E1 protein is defined, for example, on page 6, line 26 of the specification so as to include analogs and truncated forms. The definition of an HCV envelope protein moreover includes a protein with at least one epitope (see, page 3, lines 33-35 of the specification). An epitope is defined further in the specification in, for example, page 4, lines 5-8. The applicants submit the claims are definite.

The Section 112, second paragraph, rejection of claim 85 noted in paragraph 9 of Paper No. 18 is traversed. The applicants respectively submit that administering a composition of claim 79, as recited in claim 85, includes all the essential steps for immunizing of mammals, as claimed. Support for the amendment to claim 85 may be found, for example, at page 25, lines 6-7 of the specification. The Examiner's assertion that dosage of immunization, route of administration and the form of the induced immune response are required is, with due respect, submitted to be further refinements which are, perhaps, more properly the subject matter of dependent claims. Immunization requires, as an essential step, administering, as recited in claim 85. The applicants would be happy to provide examples of claims of issued U.S. patents wherein immunization only requires administration without further recitation of the details suggested by the Examiner in paragraph 9 of Paper No. 18, upon the Examiner's

further request. Withdrawal of the Section 112, second paragraph, rejection of claim 85 is requested.

The Section 101 and Section 112, first paragraph, rejection of claim 85 stated on page 4 of Paper No. 18 is traversed. Reconsideration and withdrawal of the rejection are requested as the applicants have raised monoclonal antibodies in mice, as described on page 22 and Example 7.4 (on pages 56-57 of the specification), indicating that mammals have been immunized by administering a composition according to claim 85. Accordingly, while not believed to be required, the applicants have exemplified that a mammal can be, and was, immunized by a method according to claim 85. Reconsideration and withdrawal of the Section 101 and Section 112, first paragraph, rejections of claim 85 stated on page 4 of Paper No. 18 are requested.

The Section 112, first paragraph, rejection of claims 67, 79 and 85 stated in paragraph 13 of Paper No. 18 is obviated by the above amendments. Specifically, claim 75 has been canceled, without prejudice, and the dependencies of claims 79 and 85 have been amended. Withdrawal of the Section 112, first paragraph, rejection of claims 79 and 85 stated on page 5 of Paper No. 18 is requested.

The Section 102 rejection of claims 67-68, 75, 87 and 95-96 over Matsuura is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Matsuura et al. (1992; J. Virol. 66, 1425-1431) are disclosing live recombinant vectors wherein the HCV El proteins start at a position between position 1 and position 155, and end with position 342 and that all inserted fragments allow the expression of an HCV E1 protein. As is clear from

Figure 1 in Matsuura et al., however, vectors are disclosed with HCV nucleotide sequences covering parts of the HCV polyprotein spanning amino acids 1-447, 155-447, 196-447, 224-447, 1-559 and 155-559. Each of these however fail to teach each and every aspect of the presently claimed invention. Furthermore, the constructs wherein the encoded HCV protein starts at position 196 or 224 of the HCV polyprotein (and both ending at position 447) do not result in expression of detectable amounts of the HCV E1 protein. The only allegedly relevant vector in Matsuura et al. which allows expression of a HCV polyprotein is a part spanning amino acids 155-340 (and not 342 as mentioned in Paper No. 18). The experiments described by Matsuura et al. were performed with baculovirus vectors.

The Examiner is furthermore understood to be asserting that the vectors of Matsuura et al. encode an HCV E1 protein comprising part of the claimed amino acid sequence of SEQ ID NO:7. Initially, the applicants note that, no nucleotide or amino acid sequence is disclosed in Matsuura et al., making it impossible to determine whether or not part of the claimed SEQ ID NO:7 is literally or inherently contained therein or not. As the identification of the sequence does not necessarily flow from the cited art, the identification of any sequence is not inherently contained therein such that the Section 102 rejection must be withdrawn. For completeness, the applicants note that EP 0 585 549 (National Institute of Health Japan) discloses the sequence as used by Matsuura et al. (see reference to Matsuura et al. on page 2 lines 52-53 in EP 0 585 549; copy attached) and the Examiner will appreciate that this sequence is different from SEQ ID NO:7 of the present application.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67, 75, 87 and "95-95" over Hijikata (PNAS 1991, vol. 88, pp 5547-5551), stated on page 7 of Paper No. 18 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Hijikata et al. (1991; PNAS 88, 5547-5551) are disclosing live recombinant vectors for expression of an HCV E1 protein which is a part of SEQ ID NO:7 of the current invention. Initially, the applicants submit that the vectors disclosed by Hijikata et al. are not live vectors but vectors enabling expression of a protein in a cell-free in vitro translation-transcription system. Moreover, Hijikata et al. disclose vectors for expression of parts of the HCV polyprotein spanning amino acids 1-163, 1-511, 1-740, 1-980, 124-921, 340-483, 340-696 and 340-980. The cited art therefore fails to teach each and every aspect of the presently claimed invention. The only allegedly relevant vectors in Hijikata et al. allow expression of a HCV polyprotein part spanning amino acids 1-281 and 1-381. Further, the HCV proteins expressed by Hijikata et al. are from the HCV isolate HCV-J (Kato et al. 1990, reference 4 in Hijikata et al.) which is a HCV Ia isolate. The proteins expressed in the current invention are HCV Ib proteins. The HCV sequences used in the current invention are different than those used by Hijikata et al. Thus, none of the non-live vectors disclosed in Hijikata et al. contain a part of SEQ ID NO:7. The Section 102 rejection should be withdrawn as the reference fails to teach each and every aspect of the presently claimed invention.

The Section 102 rejection of claims 67, 75, 87-88 and 95-96 over Kohura (J. Gene Virol. 1992, vol 73, pp 2313-2318) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Kohara et al. (1992; J Gen Virol 73, 2313-2318) are disclosing a live recombinant vector for expression of an HCV El protein which comprises SEQ ID NO:7 of the current invention. Kohara et al. are disclosing a HCV genomic fragment encoding the HCV polyprotein part starting at position 117 and ending at position 426. This is outside the ranges according the current invention. The experiments described by Kohara et al. were performed with vaccinia virus vectors. Furthermore, SEQ ID NO:7 is different from the sequence disclosed by Kohara et al.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67, 75, 87 and 95-96 over Hsu (Hepatology, 1993, vol. 17, pp 763-771) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Hsu et al. (1993; Hepatology 17, 763-771) are disclosing a live recombinant vector for expression of an HCV El protein which comprises a part of SEQ ID NO:7 of the current invention. Hsu et al. are disclosing vectors for the expression of part of the HCV polyprotein spanning positions 1-975, 400-950, 1-1987 or 400-1987 (see page 764, end of paragraph spanning left and right column). The reference therefore fails to teach each and every aspect of the presently claimed invention. The experiments described by Hsu et al. were performed with baculovirus vectors.

Furthermore, the HCV sequence used by Hsu et al. is derived from the HCV-H strain that is an HCV Ia isolate. SEQ ID NO:7 of the current invention is derived from a HCV Ib isolate and is different from the sequence used by Hsu et al.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67-68, 75, 87-88 and 95-96 over Devare (EP 472 207 A2) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Devare et al. (EP 0 472 207) are disclosing a live recombinant vector for expression of an HCV El protein which comprises a part of SEQ ID NO:7 of the current invention and which is just in the region of claimed HCV El starting at a position between amino acids 1-192 and ending at a position between amino acids 250-400. Devare et al. are disclosing vectors for El expression in E. coli, i.e., not live recombinant vectors. Moreover, the vectors of Devare et al. comprise HCV genomic sequences encoding parts of the HCV polyprotein spanning amino acids 114-276 (pHCV-103; column 33, lines 23-28), 263-469 (pHCV-10l; column 33, lines 53-58) and 114-469 (pHCV-104; column 35, lines 16-21). Of these, only pHCV- 103 allegedly falls within the boundaries according to the present invention. Further, the E1-encoding sequences in these vectors are different from SEQ ID NO:7. Moreover, each and every one of the E1 HCV proteins disclosed by Devare et al. is produced as a fusion protein comprising an amino-terminal CKS part of 239 amino acids followed by a linker of 7 amino acids, followed by the E1 protein and followed by a carboxyterminal peptide of 16 or 15 amino acids. The fusion proteins are not processed in order to obtain the E1 protein (or a fragment thereof) itself. These vectors thus can

not be considered as vectors for expression of E1 or a part thereof.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67-70, 73, 87 and 95-96 over Lanford et al. (1993; Virology 197, 225-235) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Lanford et al. (1993; Virology 197, 225-235) are disclosing a live recombinant vector for expression of an HCV El protein which comprises a part of SEQ ID NO:7 of the current invention. Lanford et al. are disclosing vectors for expression of E1 from part of a HCV polyprotein spanning amino acids 117-386 or 117-340. Absent any reference to HCV isolate or HCV sequence, it is impossible to state that the vectors of Lanford et al. are comprising part of SEQ ID NO:7. The experiments described by Lanford et al. were performed with baculovirus vectors.

Withdrawal of the Section 102 rejection is requested as the reference fails to literally or inherently teach the presently claimed invention.

The Section 102 rejection of claims 67, 73, 75, 87-88 and 95-96 over Chien et al. (WO 94/01778) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Chien et al. (WO 94/01778) are disclosing a live recombinant vector for expression of an HCV El protein which comprises a part of SEQ ID NO:7 of the current invention. In Example 1 of Chien et al. a vector capable of expressing Core, E1 and E2 is disclosed (not E1 or a part thereof alone, this vector comprises a part of the HCV genome encoding the amino acids 1-966

of the HCV polyprotein). This vector falls outside the scope of the current invention. Further, Example 1 only **alludes** to a yeast vector for expression of E1 (130 aa) as a fusion protein with human superoxide dismutase (not as E1 or a part thereof *per se*) but the precise boundaries and sequence of this E1 protein remains elusive. It is thus impossible to state that the vectors of Chien et al. are comprising a part of SEQ IDNO:7.

Withdrawal of the Section 102 rejection is requested as the cited reference fails to teach each and every aspect of the presently claimed invention.

The Section 102 rejection of claims 67, 73, 75, 87-88 and 95-96 over Ralston et al. (1993; J Virol 67, 6753-6761) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Ralston et al. (1993; J Virol 67, 6753-6761) are disclosing live recombinant vectors for expression of an HCV El protein which comprises a part of SEQ ID NO:7 of the current invention. From Table 1 in Ralston et al. it is clear that the vectors disclosed comprise parts of a HCV genomic sequence for expression of HCV polyprotein parts spanning amino acids 1-906 and 347-906 which fall outside the ranges of the currently claimed invention. Allegedly relevant vectors of Ralston et al. enable expression of the HCV polyprotein parts spanning amino acids 1-304 or 1-381. The experiments described by Ralston et al. were performed with vaccinia virus vectors.

The HCV-1 sequence used by Ralston et al., was a HCV type Ia isolate. The sequence from the current invention, SEQ ID NO:7, is derived from a HCV type Ib isolate and is different from the sequence in Ralston et al.

Withdrawal of the Section 102 rejection is requested as the reference fails to teach each and every aspect of the presently claimed invention.

The Section 102 rejection of claims 67, 73, 75, 87-88 and 95-96 over Grakoui et al. (1993; J Virol 67, 1385-1395) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Grakoui et al. (1993; J Virol 67, 1385-1395) are disclosing a live recombinant vector for expression of an HCV E1 protein which comprises a part of SEQ ID NO:7 of the current invention. Firstly, contrary to the statement by the Examiner "under a promoter T7", Grakoui et al. refers to the pET-3x vector (used for expression of the E1 partial protein) as "which produce N-terminal fusions with the T7 gene *10* product". The expression of such a fusion protein is clearly something completely different from expression driven by a T7 promoter. Secondly, the vectors disclosed by Grakoui et al. are vectors for expression in E. coli and are thus not live recombinant vectors. Thirdly, none of the vectors disclosed by Grakoui et al. (see Table 1) comprise a HCV nucleotide sequence enabling expression of HCV polyprotein parts within the ranges of the current invention. Fourthly, the E1-fragment expressed from the relevant vector in Grakoui et al. comprises a HCV-H nucleotide sequence. HCV-H is a type 1a isolate of HCV. SEQ ID NO:7 of the current invention, being derived from a type Ib HCV isolate, is different from the sequence in Grakoui et al.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67-68, 73, 75, 87-88 and 95-96 over Ray et al. (1994; J Virol 68, 4420-4426) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Ray et al. (1994; J Virol 68, 4420-4426) are disclosing a live recombinant vector for expression of an HCV E1 protein which comprises a part of SEQ ID NO:7 of the current invention. The E1 - fragment expressed from the relevant vector in Ray et al. comprises a HCV- 1 nucleotide sequence. HCV- 1 is a type 1 a isolate of HCV. SEQ ID NO:7 of the current invention, being derived from a type Ib HCV isolate, is different from the sequence in Ray et al. The experiments described by Ray et al. were performed with vaccinia virus vectors. The vectors comprise a HCV nucleotide sequence encoding part of the HCV polyprotein spanning amino acids 1-339.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67-70, 75, 87 and 95-96 over Watanabe et al. (US 5,610,009) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Watanabe et al. (US 5,610,009) are disclosing a live recombinant vector for expression of an HCV E1 protein starting at position 192 and ending "with amino acids 259 or 337 or 383 ... in which a carboxyl terminal was truncated at residue 260-296 to remove the internal hydrophobic region" (see, page 11 of Paper No. 18) which is part of SEQ ID NO:7 of the current invention. After analyzing the indicated passages in the description of the cited art (i.e., column 12, lines 16-29 cited by the Examiner), the applicants have concluded that the allegedly

relevant vectors for expression of E1 or parts thereof as disclosed by Watanabe et al. are:

pHCV 172: fusion protein of amyloid precursor protein (APP) and HCV polyprotein region spanning amino acids 192-383;

pHCV4 15: fusion protein of amyloid precursor protein (APP) and HCV polyprotein region spanning amino acids 192-336; and

pHCV4I6: fusion protein of pHCV4IS wherein the amino acids 260-296 have been deleted.

The internal deletion of amino acids 260-296 is not equal to or within the ranges claimed in the present invention and as outlined by the Examiner. All HCV sequences used by Watanabe et al. are derived from HCV-1, a type 1a isolate. SEQ ID NO:7 of the current invention, being derived from a type Ib HCV isolate, is different from the sequence in Watanabe et al. The experiments described by Watanabe et al. were performed with adenovirus vectors.

Withdrawal of the Section 102 rejection is requested.

The Section 102 rejection of claims 67-68, 75, 87 and 95-96 over Brechot et al. (US 5,879,904) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to be asserting that Brechot et al. (US 5,879,904) are disclosing a live recombinant vector for expression of different fragments of HCV E1 which contain part of SEQ ID NO:7 of the current invention.

The Examiner refers to col. 1 line 65 to col. 2 line 29 in Brechot et al., which relates to nucleic acid and peptide fragments of the French isolate HCV E1. Reference

to plasmids or expression vectors is made in Brechot et al. in col. 2 lines 42-45. Comparison of each and every amino acid sequence of at least 7 amino acids of SEQ ID NO:3 (covering part of Core and E1) with SEQ ID NO:7 of the current invention revealed that none of the envisaged sequences in Brechot et al. is comprised in SEQ ID NO:7.

Withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claims 67-70, 73-75, 87-88 and 95-96 over Lanford, Ralston, Watanabe and Ford (Protein expression and purification, 1991, vol. 2, pp. 95-107) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The applicants submit that were the E1 expression vectors claimed in the current invention (claims 68-70) found allowable, then any variation to the E1 proteins encoded by such expression vectors would also be allowable as claims 74 and 88 are dependent from allowable claims. The claimed invention is not taught or suggested by the combination of cited art and the Section 103 rejection should be withdrawn.

The Examiner's indication that claims 70, 76 and 77 contain allowable subject matter is acknowledged with appreciation. See, page 13 of Paper No. 18. The claims, as amended, are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:plb
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100